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GAU 1656  
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AND PROCEEDINGS BEFORE  
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July 25, 2001

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Commissioner for Patents  
Washington, D.C. 20231

Art Unit 1656

Re: U.S. Utility Patent Application  
Appl. No. 09/666,890; Filed: September 20, 2000  
For: **Nucleic Acid Marker Ladder for Estimating Mass**  
Inventor: James L. Hartley  
Our Ref: 0942.2570003/RWE/AGL

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Fee Transmittal (PTO/SB/17) (*in duplicate*);
2. Reply Under 37 C.F.R. §1.111;
3. Terminal Disclaimer Over a Prior Patent (PTO/SB/26);
4. Certificate Under 37 C.F.R. §3.73(b) w/a copy of an Assignment to Life Technologies, Inc. (1 page) and a copy of the Merger Document between Life Technologies, Inc. and Invitrogen Corporation (3 pages);
5. One (1) return postcard; and
6. Our check no. 32022 for **\$110.00** to cover the Terminal Disclaimer fee.

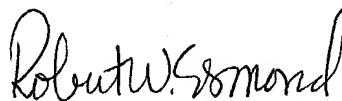
It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

Commissioner for Patents  
July 25, 2001  
Page 2

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036. A duplicate copy of this letter is enclosed.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
Attorney for Applicant  
Registration No. 32,893

RWE/AGL:kim  
Enclosures

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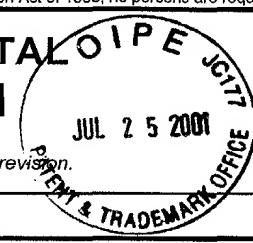
# FEE TRANSMITTAL for FY 2001

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT

(\$)

110.00



Complete if Known

|                      |                    |
|----------------------|--------------------|
| Application Number   | 09/666,890         |
| Filing Date          | September 20, 2000 |
| First Named Inventor | James L. HARTLEY   |
| Examiner Name        | Houtteman, S.      |
| Group Art Unit       | 1656               |
| Attorney Docket No.  | 0942.2570003/RWE   |

| METHOD OF PAYMENT (check one)   |   | FEE CALCULATION (continued) |              |   |                 |          |          |
|---|---|-----------------------------|--------------|---|-----------------|----------|----------|
| 1. <input type="checkbox"/> The Commissioner is hereby authorized to charge indicated fees and credit any overpayment to:   |   | 3. ADDITIONAL FEES          |              |   |                 |          |          |
| Deposit Account Number  | 19-0036                                   |                             | Large Entity | Small Entity  | Fee Description |          | Fee paid |
| Deposit Account Name  | Sterne, Kessler, Goldstein & Fox P.L.L.C. |                             |              |   |                 |          |          |
| <input type="checkbox"/> Charge Any Additional Fee Required Under 37 CFR §§ 1.16 and 1.17   |   |                             |              |   |                 |          |          |
| <input type="checkbox"/> Applicant claims small entity status<br>See 37 CFR 1.27  |   |                             |              |   |                 |          |          |
| 2. <input checked="" type="checkbox"/> Payment Enclosed: Check No. 32022  |   |                             |              |   |                 |          |          |
| <input checked="" type="checkbox"/> Check <input type="checkbox"/> Credit card <input type="checkbox"/> Money Order <input checked="" type="checkbox"/> Other*<br>*Charge any deficiencies or credit any overpayments in the fees or fee calculations of Parts 1, 2 and 3 below to Deposit Account No. 19-0036. |   |                             |              |   |                 |          |          |
| FEE CALCULATION   |   |                             |              |   |                 |          |          |
| 1. BASIC FILING FEE   |   |                             |              |   |                 |          |          |
| Large Entity Fee Code   | Fee (\$)                                  | Small Entity Fee Code       | Fee (\$)     | Fee Description   | Fee Paid        |          |          |
| 101   | 710                                       | 201                         | 355          | Utility filing fee  |                 |          |          |
| 106   | 320                                       | 206                         | 160          | Design filing fee   |                 |          |          |
| 107   | 490                                       | 207                         | 245          | Plant filing fee  |                 |          |          |
| 108   | 710                                       | 208                         | 355          | Reissue filing fee  |                 |          |          |
| 114   | 150                                       | 214                         | 75           | Provisional filing fee                                    |                 |          |          |
| SUBTOTAL (1) (\$)   |   | -0-                         |              |   |                 |          |          |
| 2. EXTRA CLAIM FEES   |   |                             |              |   |                 |          |          |
| Large Entity Fee Code   | Fee (\$)                                  | Small Entity Fee Code       | Fee (\$)     | Extra   | Fee from below  | Fee Paid |          |
| Total Claims  |   |                             |              | - 20** =  | X               | =        |          |
| Indep. Claims   |   |                             |              | - 3** =   | X               | =        |          |
| Multiple Dependent  |   |                             |              |   | =               |          |          |
| Large Entity Fee Code   | Fee (\$)                                  | Small Entity Fee Code       | Fee (\$)     | Fee Description   |                 |          |          |
| 103   | 18  | 203                         | 9            | Claims in excess of 20                                    |                 |          |          |
| 102   | 80  | 202                         | 40           | Independent claims in excess of 3                         |                 |          |          |
| 104   | 270                                       | 204                         | 135          | Multiple dependent claim                                  |                 |          |          |
| 108   | 80  | 209                         | 40           | **Reissue independent claims over original patent         |                 |          |          |
| 110   | 18  | 210                         | 9            | **Reissue claims in excess of 20 and over original patent |                 |          |          |
| SUBTOTAL (2) (\$)   |   | -0-                         |              |   |                 |          |          |
| *Reduced by Basic Filing Fee Paid   |   |                             |              |   |                 |          |          |
| SUBTOTAL (3) (\$)   |   |                             |              |   |                 |          |          |
| 110.00  |   |                             |              |   |                 |          |          |

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Complete (if applicable)

| SUBMITTED BY      |                  |                                   |        |           |               |
|-------------------|------------------|-----------------------------------|--------|-----------|---------------|
| Name (Print/Type) | Robert W. Esmond | Registration No. (Attorney/Agent) | 32,893 | Telephone | 202-371-2600  |
| Signature         | Robert W. Esmond |                                   |        | Date      | July 25, 2001 |

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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JUL 27 2001

TECH CENTER 1600/2900

In re application of:

James HARTLEY

Appl. No. 09/666,890

Filed: September 20, 2000

For: **Nucleic Acid Marker Ladder for  
Estimating Mass**

Art Unit: 1656

Examiner: S. Houtteman

Atty. Docket: 0942.2570003/RWE/AGL

#7

M.J.G

7/30/01

### Reply Under 37 C.F.R. § 1.111

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

In reply to the Office Action dated April 25, 2001 (PTO Prosecution File Wrapper Paper No. 6), Applicant submits the following Remarks.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

### *Remarks*

Reconsideration and withdrawal of the outstanding rejections are respectfully requested. Claims 15-33 are now pending in this application with claims 15, 23 and 31 being the independent claims. Reconsideration of claims 15-33 is respectfully requested.

James HARTLEY  
Appl. No. 09/666,890

**I. The Rejection under Obviousness-Type Double Patenting over the '201 Patent**

Claims 15-33 have been rejected by the Examiner under the doctrine of obviousness-type double patenting over the claims of U.S. Patent No. 5,834,201 ("the '201 patent"). Applicant respectfully traverses this rejection. Enclosed herewith is a Terminal Disclaimer to Obviate a Double Patenting Rejection Over a Prior Patent and Certificate Under 37 C.F.R. § 3.73(b).

In view of the terminal disclaimer and Certification, Applicant submits that the rejection is now moot. Withdrawal of the rejection is respectfully requested.

**II. The Rejection under 35 U.S.C. § 103(a) Over Carlson in view of Hartley, Mullis and Maniatis**

Claims 15-33 have been rejected by the Examiner under 35 U.S.C. § 103(a) as allegedly obvious over Carlson *et al.*, European Patent Application No. 0 466 404 ("Carlson") in view of Hartley *et al.*, *Gene* 13:347-353 (1981) ("Hartley"), Mullis *et al.*, U.S. Patent No. 4,683,195 ("Mullis") and Maniatis *et al.*, MOLECULAR CLONING: A LABORATORY MANUAL, 468-469 (1982) ("Maniatis"). Applicant respectfully traverses this rejection.

There is no motivation in the prior art to combine the references in the manner proposed by the Examiner. Rather, it is only by using the claims of the subject application as a template that the Examiner has sifted through the various references in the prior art and cited certain portions thereof in an attempt to reconstruct the claimed invention.

For example, the Examiner has alleged that "Hartley et al. teaches this ladder wherein the integer is 123. Hartley states 'it should be possible to polymerize any DNA

segment by this method'." Such an allegation, however, incorrectly characterizes the teachings of Hartley.

Contrary to the Examiner's allegation, Hartley does not relate to DNA marker ladders, *i.e.*, mixtures of DNA fragments for use as calibration standards in gel electrophoresis. Rather, Hartley is directed to a "method for the insertion of multiple copies of a DNA segment into a plasmid and subsequent cloning of the plasmid . . . ." The potential uses of this method are disclosed as including "production of large amounts of small, homogeneous DNAs for physical studies such as X-ray crystallography, and increasing the expression of cloned genes in bacteria." Thus, Hartley is not even remotely relevant to the presently claimed invention.

More specifically, a reference is reasonably pertinent to the problem being solved if, and only if, "it is one which, because of the [subject] matter with which it deals, [would] logically have commended itself to an inventor's attention in considering his problem." *In re Clay*, 966 F.2d 656, 659, 23 USPQ2d 1058, 1061 (Fed. Cir. 1992). The Hartley reference cited by the Examiner does not satisfy this standard.

In the present case, the present Applicant was seeking a DNA marker ladder that could be used as a reference standard for determining both the size of an unknown DNA molecule and the amount thereof in a sample. The Hartley reference, however, was seeking a method for insertion of multiple copies of a particular DNA segment, such as a gene, into a plasmid to increase subsequent expression of that DNA segment in a host organism. One of ordinary skill in the art preparing a marker ladder capable of calibrating both the size and amount of DNA in a sample simply would not look to a

reference that relates to polymerizing a particular gene for insertion into an expression vector.

Similarly, there is no motivation to combine Maniatis with the other references in the manner proposed by the Examiner. Indeed, for at least the following two reasons, one skilled in the art would not have been motivated to combine Maniatis with Carlson.

First, Maniatis expressly teaches that “[t]he standard DNA solution [in a gel electrophoresis assay for determining the quantity of DNA in a sample] should contain a *single* species of DNA, approximately the same size as the unknown DNA.” The use of a single strand of DNA as the reference standard is critical to the method disclosed by Maniatis because that method requires the concentration of DNA in a given lane in the assay to be known (so that the concentration of the amount DNA can be determined by direct comparison of the relative intensity of their respective fluorescence).

In striking contrast to Maniatis, however, Carlson employs DNA marker ladders in a gel electrophoresis assay to determine the size of an unknown DNA molecule, *i.e.*, the size of the unknown DNA is calculated by comparing the distance it migrates to the distances migrated by DNA molecules of known size. As described both in Carlson and the above-identified application, such DNA marker ladders are composed of a *mixture* of many DNA fragments of varying size. A mixture of DNA fragments is important so that the unknown DNA can be compared to a number of DNA fragments of differing size -- the more fragments available for comparison, the more accurate the resulting estimate of size is likely to be. Indeed, Carlson strongly suggests a preference for high numbers of DNA fragments in any given ladder, stating that “[t]he number of [DNA fragments] pooled is at least 5, preferably at least 10, more preferably at least 15, yet more preferably

at least 20, and most preferably at least 25." Moreover, Carlson does disclose a marker ladder comprising an endonuclease digest, Carlson, however, does not teach that the relative concentrations of the fragments can be controlled during digestion to produce a marker ladder capable of quantifying the amount of DNA present in a sample, like the presently claimed marker ladder.

Secondly, Maniatis specifically teaches staining with ethidium bromide for visualizing the reference DNA and the sample DNA and thereby determining by comparison the amount of DNA in the sample. Conversely, however, Carlson expressly teaches that ethidium bromide staining should *not* be used as a method of visualization when using an endonuclease digest marker ladder because "the ladder DNA may appear as a "smear" due to the multitude of fragments." Such smearing is strongly disfavored as it makes comparison of the unknown DNA with the reference DNA very difficult and prone to error.

The respective teachings above are so divergent, indeed, even to the point of teaching away from one another, that there is no motivation to combine these references as proposed by the Examiner. One skilled in the art, possessing either Maniatis or Carlson, would plainly not look to the other in seeking to modify one simply because the teachings thereof directly contradict the teachings in the first (the ordinary artisan, however, is one who thinks along the lines of conventional wisdom in the art, not one who seeks to innovate or experiment; *see Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 227 USPQ 293 (Fed. Cir. 1985)).

In light of their contradictions and inconsistencies, anyone trying to combine Maniatis with Carlson would clearly be working *outside* the lines of conventional

wisdom in the art. It is wholly improper to combine two references when the references themselves teach away from that combination, as do Maniatis and Carlson, and such a combination is not obvious. *In re Graselli*, 713 F.2d 731, 218 USPQ 769 (Fed. Cir. 1983).

With respect to the citation of Mullis, simply because a technique is available to one of ordinary skill in the art to place restriction sites in a nucleic acid molecule, this does not render obvious the presently claimed marker ladder or even a nucleic acid molecule having internal restriction sites (such as the one from which the claimed marker ladder is generated). To the contrary, there must still be some suggestion in the prior art that suggests the compound in order to make out a *prima facie* case. *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995). A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be performed. *Id.* at 1554, 34 USPQ2d at 1216.

In view of the above discussion of the references, it is clear that hindsight is required to interpret the cited references and select certain teachings thereof in an attempt to reconstruct the presently claimed invention. Such hindsight, however, is no substitute for the requisite motivation necessary to sustain a rejection for obviousness under § 103.

The final requirement of every *prima facie* case of obviousness is that the combined references must teach *every limitation* of the claims. MANUAL OF PATENT EXAMINING PROCEDURE § 2143.03 (Rev. 1, February 2000); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1990) (“[f]ocusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness”).

In the present case, however, even if the teachings of the references cited by the Examiner were combined, that combination does not teach or suggest each and every limitation of the various claimed embodiments of the present invention.

In addition to the factors required to establish a *prima facie* case of obviousness, a conclusion of obviousness *vel non* is based on a totality of the evidence. Accordingly, before obviousness can be found, secondary considerations which may not be immediately apparent from the express language of the claims, such as the particular advantages of the claimed invention, must be evaluated. *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). These secondary considerations must be considered as a whole along with the initial facts on which the Examiner's *prima facie* case was based, *i.e.*, the secondary considerations should not be regarded as a rebuttal of the Examiner's position, but rather a final determination of obviousness must be made considering the entire record. *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990).

Of particular importance are the unique advantages of the inventive marker ladder. It must be remembered that

[w]hen prior art references require selective combination by a court to render obvious a subsequent invention, there must be some reason for the combination other than hindsight gleaned from the invention itself. There must be "something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination."

*Critical to the analysis is an understanding of the particular results achieved by the new combination.*

*Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985)(citations omitted; emphasis supplied).

As described in the specification of the present application, the inventive marker ladder is useful as a calibration standard in electrophoresis. *Specification*, page 9, lines 9-10. Because the sizes of the various fragments that make up the inventive ladder are multiples of an integer, the presently claimed invention is extremely convenient and easy to use and so allows the ordinary artisan to quickly calculate the size of an unknown nucleic acid fragment. *Id.* at lines 10-13. The presently claimed marker ladder, however, *also* allows the ordinary artisan to determine the mass of the unknown nucleic acid, *i.e.*, how much of the unknown nucleic acid is present in the sample being tested. *Id.* at lines 14-16.

This latter feature is possible because all of the fragments that compose the inventive marker ladder are generated from a *single* nucleic acid molecule, the resultant fragments are present in known proportions to one another. *Id.* at lines 17-21. If a skilled artisan made the fragments separately and then mixed those fragments to form a marker ladder, that worker would need to measure the concentration of each fragment as well as the volume of that fragment added to the ladder mixture. All of these concentration and volume measurements represent a substantial increase in the labor necessary to prepare a nucleic acid marker ladder as well as providing significant additional opportunities for the introduction of errors. Such systematic errors are *absent* when using the inventive marker ladder.

This advantageous combination of measurements, *i.e.*, measurement of both the size of an unknown nucleic acid fragment and the concentration of that unknown

fragment in a mixture, that can be obtained in a *single* experiment using the inventive marker ladder is not suggested by or apparent from the Examiner's combination of references. An evaluation of the obviousness of a claimed combination requires consideration of the results achieved with that combination. *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1990). Thus, even if, *arguendo*, a *prima facie* case of obviousness has been established, the discovery that the inventive marker ladder enables a single assay to determine both the size and concentration of unknown DNA in a sample, without the systematic errors associated with prior art assays, plainly refutes any such *prima facie* case.

Claims 15-33 are in condition for immediate allowance. An early indication of allowance is therefore respectfully solicited.

### ***III. Conclusion***

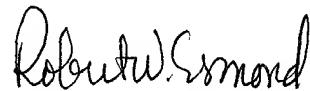
All of the stated grounds of rejections have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding objections and rejections. Applicant believes that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. Prompt and favorable consideration of this Amendment is respectfully requested.

James HARTLEY  
Appl. No. 09/666,890

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
Attorney for Applicant  
Registration No. 32,893

Date: July 25, 2001

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